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The continuing search for antitumor agents from higher plants

Li Pan, Heebyung Chai, and A. Douglas Kinghorn*

Division of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, The Ohio State University, OH 43210, USA

Abstract

Plant secondary metabolites and their semi-synthetic derivatives continue to play an important role in anticancer drug therapy. In this short review, selected single chemical entity antineoplastic agents from higher plants that are currently in clinical trials as cancer chemotherapy drug candidates are described. These compounds are representative of a wide structural diversity. In addition, the approaches taken toward the discovery of anticancer agents from tropical plants in the laboratory of the authors are summarized. The successful clinical utilization of cancer chemotherapeutic agents from higher plants has been evident for about half a century, and, when considered with the promising pipeline of new plant-derived compounds now in clinical trials, this augurs well for the continuation of drug discovery research efforts to elucidate additional candidate substances of this type.

Keywords

Higher plants; secondary metabolites; anticancer agents; compounds in clinical trials; antineoplastic drug discovery

1. Introduction

Cancer is one of the leading causes of death in both developed countries and developing countries and is therefore of worldwide concern. According to global cancer statistics released by the American Cancer Society, the total number of deaths from cancer in 2007 was 7.6 million, or about 20,000 deaths each day, with 38% in developed countries and 62% in developing countries. By 2050, 27 million new cancer cases and 17.5 million cancer deaths are projected to occur in the world (American Cancer Society, 2007). Accordingly, much effort has been made to develop various approaches to reduce the threat caused by cancer.

Chemotherapy is an important option in modern cancer treatment, and many clinically available anticancer drugs, of synthetic or natural product origin, are currently used to treat some types of leukemias, lymphomas and solid tumors (Chabner et al., 2005; DeVita et al., 2008). A recent analysis of the anticancer drug market in North America, Europe, and Japan during the period 1981 to 2006 revealed that 47.1% of a total of 155 clinically approved anticancer drugs were either unmodified natural products or their semi-synthetic derivatives, or synthesized molecules based on natural product compound pharmacophores (Newman and Cragg, 2007). Natural products, characterized as small-molecule secondary metabolites that originate from terrestrial and marine plants, microorganisms and animals, tend to present more structurally diverse “drug-like” and “biologically friendly” molecular qualities than pure synthetic compounds at random, and are an important source of novel lead structures for the synthetic and combinatorial chemistry aspects of anticancer drug discovery (Bindseil et al., 2001; Firn and Jones, 2003; Vuorela et al., 2004). Despite certain technical limitations

*Corresponding author. Tel.: +1-614-247-8094; Fax: +1-614-247-8642. kinghorn.4@osu.edu (A. D. Kinghorn)..

inherent in the investigation of the small-molecule organic constituents of organisms using modern drug discovery platforms, improvements in automated high-throughput bioactivity screening techniques and technologies applied in the processes of compound analysis, purification, and structural identification have significantly speeded up the natural product bioassay-guided fractionation procedure (Koehn and Carter, 2005; Potterat and Hamburger, 2006; Anonymous, 2007). The application of biotechnological methods has allowed selected natural product metabolites to be produced in a relatively controlled manner, and to be less limited by sourcing problems caused by environmental, seasonal and geographical effects (Fischbach and Walsh, 2006). It has been concluded recently that natural products from all types of organisms offer an “unlimited” resource for future drug discovery (Li and Vederas, 2009).

For millennia, terrestrial plants have been used as a prominent source of medicines, and their early use in this regard in Ancient Egypt, India, China, and the Arab world has been documented (Sneader, 2005). In a volume summarizing a series of review articles that appeared previously in the journal *Lloydia* by the late Dr. Jonathan L. Hartwell, then at the U.S. National Cancer Institute, more than 3000 plant species were described with evidence of previous use for treating cancer (Hartwell, 1982). However, it must be pointed out that cancer is not easy to be diagnosed in a reliable manner like certain other diseases such as skin infections and gastrointestinal disturbances, so claims of efficacy in treating cancer by plants used in traditional medicine should be treated with some skepticism (Cragg et al., 2009). Despite this reservation, there are now four major structural classes of plant-derived compounds used in western medicine as single chemical entity compounds, namely, the vinca alkaloids (vinblastine, vincristine, vinorelbine), the epipodophyllotoxin lignans (etoposide, teniposide, etoposide phosphate), the taxane diterpenoids (paclitaxel, docetaxel), and the camptothecin quinoline alkaloid derivatives (topotecan, irinotecan), as listed in order of their introduction to established oncology therapy in the United States (Chabner et al., 2005; DeVita et al., 2008). Since a detailed treatment of these four classes of plant-derived agents has appeared in the literature recently (Cragg et al., 2005), these compounds will not be further discussed in the present review. However, it should be noted that the contributions of pioneering natural product chemists in North American academic, governmental, industrial, and private research institutions were instrumental in the isolation and/or structure elucidation of the key lead compounds vinblastine (1) (Noble et al., 1958; Svoboda et al., 1959; Neuss et al., 1962), vincristine (2) (Svoboda, 1961; Neuss et al., 1962), podophyllotoxin (3) (Hartwell and Schecker, 1951), paclitaxel (originally taxol, 4) (Wani et al., 1971), and camptothecin (5) (Wall et al., 1966). The antineoplastic activities of these five lead compounds were discovered through systematic laboratory studies, rather than relying on ethnomedical observations on their respective plant of origin (Fabricant and Farnsworth, 2001).

In the following sections of this short review, we will provide a brief overview of a number of plant-derived substances currently under clinical trial as antineoplastic drug candidates. Approaches taken towards the discovery of anticancer agents from tropical plants, as carried out in the laboratory of the authors, will be described, prior to some concluding remarks. It must be considered that, in the last fifty years, most new drugs of natural origin have been obtained from soil microorganisms, terrestrial fungi, and higher plants (Kinghorn, 2008). However, there is now a sizeable pipeline of about 25 potential anticancer drugs of marine origin presently in clinical trials, and the first of these, ecteinascidin (trabectedin) is used clinically to treat soft tissue sarcoma in Europe (Sashidhara et al., 2009). Therefore, a central question to be posed is whether or not it is desirable to continue to search for potential new anticancer compounds from terrestrial higher plants specifically, or if it would be preferable to de-emphasize this work in order to concentrate available research resources on natural products derived from other types of organisms for this purpose, such as those of marine origin.

2. Selected plant-derived antineoplastic agents in clinical trials

Natural products continue to be an invaluable resource of anticancer drug discovery in recent years, by considering the comparatively large number of chemical entities of natural origin currently under clinical trials (Corson and Crews, 2007; Butler, 2008; Harvey, 2008; Saklani and Kutty, 2008; Sashidhara et al., 2009). In the paragraphs below, plant-derived oncology drug candidates, now in clinical trials, will be considered specifically. Presently, a large number of derivatives of paclitaxel and camptothecin are in clinical trials to treat various types of cancer, with, among these, several taxanes [ABI-007 (suspension), DHA-paclitaxel, paclitaxel poliglumex, RPR-116278A, XRP-9881 (RPR109881A)] and camptothecin derivatives [9-aminocamptothecin, exatecin mesylate, oral topotecan, rubitecan (9-nitrocamptothecin)] being the most advanced, and in Phase III clinical trials (Saklani and Kutty, 2008). Two additional vinca alkaloid derivatives are also in phase clinical trials (vinflunine ditartrate and anhydrovinblastine) as well as two epipodophyllotoxin derivatives (NK-611 and tafluposide) (Saklani and Kutty, 2008). In the paragraphs following, selected plant-derived compounds of structural types other than of the vinca alkaloid, epipodophyllotoxin, taxane, and camptothecin classes will be highlighted in alphabetical order, in order to further emphasize the structural diversity of promising candidate drug molecules from plants as potential cancer chemotherapeutic agents. Several of the compounds to be mentioned are obtained from traditional Chinese medicine (TCM).

In the 1980s, Pettit and colleagues at Arizona State University isolated several groups of structurally simple stilbenoid compounds from the South African tree, *Combretum caffrum* Kuntze (Combretaceae), called the combretastatins (Pettit et al., 1982; 1987). The combretastatins comprise several series of related compounds, with the A series being *cis*-stilbenes active *in vitro* against the leukemic P388 and L1210 cell lines (Pinney et al., 2005). Combretastatin A4 phosphate (6, CA4P) is a water-soluble prodrug of the natural stilbenoid, combretastatin A4 (7) (Young and Chaplin, 2004; Pinney et al., 2005). Compound 6 is the prototype compound of a new class of antineoplastic agents being developed as tubulin-binding vascular targeting agents (VTAs), which can induce morphological changes within endothelial cells and lead to rapid and selective vascular dysfunction in tumors (Young and Chaplin, 2004; Delmonte and Sessa, 2009). CA4P (6), both alone, and in combination with established chemotherapeutic agents, is being investigated in phase II clinical trials for the treatment of anaplastic thyroid carcinoma and other forms of cancer in the United States (Pinney et al., 2005; ClinicalTrials.gov, 2009a,b).

Curcumin (8), a yellow polyphenol pigment isolated from *Curcuma longa* L. (Zingiberaceae) also known as turmeric, has a long history of utility in South Asia not only as a dietary supplement but also for healthcare (Singh, 2007). A broad spectrum of activities has been attributed to curcumin including antioxidant, antiinflammatory, antimicrobial, and immunomodulatory effects as well as potential antitumor effects. Curcumin inhibits proliferation of a wide variety of malignant cells through regulating numerous intracellular signaling pathways, by acting on various targets, including transcription factors, growth factor receptors, cell surface adhesion molecules, and protein kinases (Aggarwal et al., 2007). A phase II clinical trial of curcumin (8) in patients with advanced pancreatic cancer has been launched at the M. D. Anderson Cancer Center in Houston, Texas (Dhillon et al., 2008).

Homoharringtonine (9, HHT, Ceflatonin®) is a *Cephalotaxus* alkaloid isolated from several *Cephalotaxus* species indigenous to eastern Asia. Compound 9 was isolated in the early 1970s from *Cephalotaxus harringtonia* (Knight ex J. Forbes) K. Koch (Cephalotaxaceae) by Powell and colleagues, at the United States Department of Agriculture facility at Peoria, Illinois, along with three structurally similar, naturally occurring cephalotaxine esters, inclusive of harringtonine (10) (Powell et al., 1972). Compound 9 remains the most promising antileukemic

agent of numerous structurally related compounds, including many semisynthetic derivatives, due to its natural abundance and potent biological activity. This alkaloid induces the differentiation and apoptosis of cancer cells by inhibiting protein synthesis at the ribosome level (Luo et al., 2004; Meng et al., 2008). Homoharringtonine (9) as a single chemical entity is currently under phase II/III clinical trials for the treatment of patients with chronic myeloid leukemia (CML) in the United States and Europe (Itokawa et al., 2005; Quintas-Cardama et al., 2007; The Rocky Mountain Blood and Marrow Transplant Program, 2009). A mixture of homoharringtonine (9) and harringtonine (10) has been used clinically for the treatment of acute myeloid leukemia (AML) in the People's Republic of China for some time (Kantarjian, 2001; Itokawa et al., 2005). Homoharringtonine (9) has also been evaluated in clinical trials for additional forms of leukemia and for some solid tumors (Itokawa et al., 2005).

Indigo (11) and its isomer, indirubin (12), are two *bis*-indole alkaloids found in a traditional Chinese medicine called “Qingdai” (Indigo Naturalis), which has been used in mainland China for the treatment of eczema, hematemeses, tumefaction, and other conditions (Zhongyaoshijia, 2009). “Qingdai” is composed of several plant species containing a dark blue dye, including the leaves and/or stems of *Baphicacanthus cusia* (Nees) Bremek. (Acanthaceae), *Indigofera tinctoria* L. (Fabaceae), *Indigofera suffruticosa* Mill. (Fabaceae), *Isatis tinctoria* L. (Brassicaceae), and *Polygonum tinctorium* Ait. (Polygonaceae) (Deng, 1986). Indirubin (12) has been reported to possess cyclin-dependent kinase (CDK) inhibitory potential, and broad-spectrum antitumor activity (Eisenbrand et al., 2004). Meisoindigo (13) is an indirubin derivative, developed to increase the solubility in water and reduce the side effects of indirubin. This compound showed significant activity against cancer cells through an ability to inhibit cyclin-dependent kinases, induce cell differentiation, promote apoptosis, and arrest cells in the G0/G1 phase of the cell cycle, and it also inhibited tumor growth in HT-29 colon cancer xenografts (100 mg/kg, i.p.) (Zuo et al., 2008). Meisoindigo is undergoing a phase III clinical trial in the People's Republic of China for the treatment of chronic myelogenous leukemia (CML) (Cooperative Study Group of Phase III Clinical Trial on Meisoindigo, 1997).

Perillyl alcohol (14), a widely distributed limonene-type monoterpenoid, is found from the essential oils of some aromatic herbs, such as lavender (*Lavandula x intermedia*, Lamiaceae), peppermint (*Mentha x piperita* L., Lamiaceae), spearmint (*Mentha spicata* L., Lamiaceae), and celery seeds (*Apium graveolens* L. Apiaceae) (Belanger, 1998). The observed effects of perillyl alcohol include the induction of apoptosis, differentiation, and cell cycle arrest in the G1 phase, through the regulation various cellular substances that are involved in cell growth and differentiation (Peffley et al., 2007; Yeruva et al., 2007). A phase II clinical trial sponsored by the U.S. National Cancer Institute (NCI) to study the effectiveness of perillyl alcohol in treating patients with metastatic breast cancer refractory to previous chemotherapy has been conducted (Bailey et al., 2008).

Phenoxodiol (15), derived from genistein (16), a natural isoflavone constituent of the soybean [*Glycine max* (L.) Merr.; Fabaceae]. Phenoxodiol has been promoted as a new promising drug candidate in oncology for its broad anticancer spectrum and minimal toxicity (Choueri et al., 2006; Butler, 2008). As a multiple signal transduction regulator, phenoxodiol leads to mitotic arrest and apoptosis of tumor cells through multiple mechanisms such as decreasing the level of antiapoptotic proteins and inhibiting the activity of DNA topoisomerase (topo) II (Constantinou and Husband, 2002; Choueiri et al., 2006). Compound 15 is under advanced clinical trial for development as a “chemosensitizer” when combined with platinum drugs for the treatment of ovarian cancer, and as a monotherapy for cervical and prostate cancers (Mor et al., 2006; Silasi et al., 2009). There is also an interest in developing genistein (16) as an antileukemic agent (Raynal et al., 2008).

Protopanaxadiol [17; 20S-protopanaxadiol (PPD)] is a dammarane-type triterpene aglycone derived by hydrolysis of certain saponins from ginseng [*Panax ginseng* C.A. Mey.; Araliaceae]. Protopanaxadiol has demonstrated effects on apoptosis induction in cancer cells and cell cycle arrest through various signaling pathways including caspases, and has also been found to show cytotoxic activity against multidrug-resistant tumors by acting as an effective P-glycoprotein blocker (P-gp, MDR1) (Popovich and Kitts, 2002; Li et al., 2006; Liu et al., 2007).

Protopanaxadiol (17, under the trade name Pandimex™), is now in a Phase I clinical trial launched by PanaGin in the United States for the treatment of lung cancer and other solid tumors (Saklani and Kutty, 2008; Panagin Pharmaceuticals, Inc., 2009). In addition, it has been approved conditionally in mainland China for the treatment of advanced cancers of the breast, colon-rectum, lung, and pancreas (PanaGin Pharmaceuticals, Inc., 2009).

Triptolide (18; PG490), is a diterpenoid triepoxide isolated from *Tripterygium wilfordii* Hook.f. (Celastraceae), which is a perennial woody vine distributed in eastern Asia, with a long history of use in traditional Chinese medicine for the treatment of immune-related disorders and inflammation (Ramgolam et al., 2000). Besides the anti-inflammatory and immunosuppressive properties ascribed to triptolide, it is also reported that this compound exhibits antitumor effects and induces apoptosis by modulating p53 and related proteins in a broad range of malignant cell lines (Kiviharju et al., 2002). PG490-88Na (19; 14-succinyl triptolide sodium salt), a water-soluble prodrug of PG490, which is metabolized into triptolide *in vivo* after intravenous administration, has entered Phase I clinical trials for patients with solid tumors (Kiviharju et al., 2002; Fidler et al., 2003; Saklani and Kutty, 2008).

Saporthoquinone (20), a diterpenoid quinone isolated from *Salvia prionitis* Hance (Lamiaceae), a native herb in the southern part of mainland China, is used as therapy in TCM for the treatment of fever, tonsillitis, pneumonia, and diarrhea (Xu, 1990). Salvicine (21), a semi-synthetic analog of compound 20, was found to exhibit significant growth inhibitory activity against a wide spectrum of human cancer cells *in vitro*, and showed effects in *in vivo* xenograft models bearing S-180 sarcoma, Lewis lung, A-549 lung, and LAX-83 lung adenocarcinoma cells (Zhang et al., 1999). Salvicine also demonstrated a potent cytotoxic effect on multidrug-resistant (MDR) tumor cells (Miao et al., 2003). Salvicine exerts its antineoplastic effects by acting as a non-intercalative topoisomerase II inhibitor that induces apoptosis. Salvicine (21) has entered phase II clinical trials for the treatment of solid tumors in mainland China (Cai et al., 2008).

3. Approach to the Discovery of Anticancer Agents from Plants

While the pharmaceutical industry has had a long track-record of success in developing natural product drugs for the oncology market, for more than half a century there has also been an active interest in the systematic screening of extracts from plants and other organisms for their potential anticancer activity by the U.S. National Cancer Institute (NCI) (Suffness and Douros, 1982; Cragg et al., 1999; 2006). In initial work during the period 1960-1982, over 114,000 plant-derived extracts were screened through a combination of prescreens, cell-based (cytotoxicity) screens, and *in vivo* testing in mice implanted with tumors (Suffness and Douros, 1982). During the period 1986-2004, the Natural Products Branch of the Developmental Therapeutics Program (DTP) at NCI organized the collection of some 60,000 higher plant samples in various targeted tropical locations of the world. Extracts of these plant samples were evaluated first against a pre-screen, with active samples then tested against a 60-cell line tumor panel derived from nine cancer types, followed by further *in vivo* evaluation when merited (Cragg et al., 1999; 2006). Since 1999, the prescreen was modified to screening through a three-cell panel, constituting MCF-7 breast, NCI-H460 lung, and SF-268 CNS cancer cells (Cragg et al., 1999; 2006). Although taxol (now known as paclitaxel) was discovered in the laboratory of the late Dr. Monroe Wall and Dr. Mansukh Wani at Research Triangle Institute,

North Carolina (Wani et al., 1971), the plant of origin of this compound (the bark of *Taxus brevifolia* Nutt.) was collected in Washington State initially as part of a plant collection program organized by the USDA for the NCI (Cragg et al., 1999).

In the 1980s, the U.S. National Cancer Institute set up a mechanism for funding collaborative teams from academia and industry via the “National Cooperative Drug Discovery Groups” (NCDDG) mechanism, directed toward the discovery of novel anticancer agents of synthetic and natural origin (Hallock and Cragg, 2003). While at the University of Illinois at Chicago, the senior author of this review served as a Principal Investigator for a NCDDG project (1995-2005) aimed at investigating new cancer chemotherapeutic agents from mainly tropical plants, with the other partners being Research Triangle Institute, Research Triangle Park, North Carolina and Bristol-Myers Squibb, Princeton, New Jersey. For an initial five-year period of this NCDDG funding award (1990-1995), the industrial partner was Glaxo-Wellcome Medicines Research Center, Greenford, Middlesex, U.K. In previous reviews, our group has described the general technical approaches taken towards plant collections (including intellectual property agreement development), phytochemical procedures, known compound dereplication methods, *in vitro* cell-based and mechanism-based bioassay systems, and *in vivo* assays that were used in our NCDDG project (Kingham et al., 1999; Kinghorn et al., 2003; Balunas and Kinghorn, 2005), as well as those used in a follow-up program project, also funded by the U.S. NCI (Kingham et al., 2009). We have found the *in vivo* hollow fiber assay useful as a discriminatory procedure in helping to prioritize compounds active in preliminary *in vitro* biological test systems for evaluation in mouse xenograft systems (Mi et al., 2009). The *in vivo* hollow fiber assay was originally developed at the U.S. NCI (Hollingshead et al., 1995). While a large number of compounds were obtained from tropical plants in our work that showed activity in one or more *in vitro* or *in vivo* bioassays (Kingham et al., 1999; 2003; 2009), two examples of promising antineoplastic compounds that were obtained will be featured in the following paragraphs.

The lupane-type triterpenoid, betulinic acid (22) was isolated in our NCDDG project from *Ziziphus mauritiana* Lam. (Rhamnaceae), collected in Zimbabwe. Although known already as a phytochemical of widespread distribution in the plant kingdom, betulinic acid was found to selectively inhibit the growth of human melanoma cell lines by causing apoptosis, and also exhibited activity *in vivo* for athymic mice bearing human melanoma cells (Pisha et al., 1995). Betulinic acid has also been shown to be cytotoxic to neuroectodermal and malignant brain tumor cell lines (Cichewicz and Kouzi, 2004). The compound can be produced by semi-synthesis from its abundant naturally occurring analog, betulin (23) (Alakurtii et al., 2006). An ointment containing 20% of betulinic acid is currently under phase I/II clinical trials launched by NCI as a potential therapy for the treatment of dysplastic melanocytic nevi (U.S. National Institutes of Health, 2009).

Silvestrol (24), a rocaglate derivative, was first characterized structurally and stereochemically from the tropical plant *Aglaia foveolata* Pannell (Meliaceae) in 2004, along with its 5''S epimer, episilvestrol (25), using a combination of spectroscopic data interpretation and X-ray crystallography (Hwang et al., 2004). Compounds 24 and 25 may be distinguished with other rocaglates in having a unique 1,4-dioxanyloxy group affixed to the cyclopenta[*b*]benzofuran moiety (Kim et al., 2006). The first rocaglate, rocaglamide, was reported in the literature less than 30 years ago, so this is a relatively recently discovered class of plant secondary metabolites (King et al., 1982). Silvestrol was found to possess comparable cytotoxic activity against several human cancer cell lines to those of the well-known anticancer compounds, paclitaxel (Taxol) and campothecin, and was further found to be active in the *in vivo* hollow fiber assay and the P-388 lymphocytic leukemia test system *in vivo*, when administered both ip and sc (Hwang et al., 2004). Furthermore, this promising anticancer candidate was found to exhibit B-cell selectivity in both chronic lymphocytic leukemia *in vitro* and acute lymphocytic

leukemia *in vivo* models (Lucas et al., 2009). The antineoplastic activity of silvestrol is associated with increased apoptosis, decreased proliferation, and inhibition of angiogenesis, and it acts as a strong translation inhibitor of malignancy-related mRNA by modulating the activity of initiation factor eIF4A (Bordeleau et al., 2008; Cencic et al., 2009). Silvestrol has also been reported as an antineoplastic constituent of *Aglaia leptantha* Miq. collected in Sarawak, Malaysia, although its stereochemistry was not established in this work (Meurer-Grimes et al., 2004). Silvestrol (24) has been totally synthesized by two independent groups (Gerard et al., 2007; El Sous et al., 2007; Adams et al., 2009). Further preclinical testing of silvestrol (24) as a potential antileukemic agent is currently underway.

4. Future Prospects

There is an impressive number of higher plant-derived anticancer drugs of diverse structural types both in present clinical use and as antineoplastic candidates undergoing clinical trials (Cragg et al., 2005; Butler, 2008; Saklani and Kutty, 2008). This suggests that higher plants will continue to be an important and valuable resource for anticancer drug discovery, especially since 300,000-500,000 such species are known, and these represent about 15% of the taxonomically authenticated global organism biodiversity (Tan et al., 2006). Moreover, probably less than 20% of the known plants on earth have ever been subjected to laboratory investigation for potential therapeutic effects, and a smaller percentage still for possible anticancer activity (Cragg et al., 2009). In recent years, an intriguing observation has been that fungal endophytes occur on host plants that produce anticancer lead compounds, and themselves biosynthesize the same substances. Recent examples of this phenomenon are podophyllotoxin (3) (from *Phialocephala fortunei* growing on *Podophyllum peltatum* L.) (Eyberger et al., 2006) and camptothecin (5) [from a fungus in the family Phymomyces growing on *Nothapodytes foetida* (Wight) Sleumer] (Puri et al., 2005). Laboratory manipulation of endophytic fungi that produce important biological molecules may lead to more reliable supplies of rare anticancer agent lead compounds of plant origin in the future.

While the pipeline of potential anticancer agents from plants is promising, the same can be said for interesting new natural product leads to treat cancer from terrestrial microbes and marine organisms (Cragg et al., 2005; 2009; Butler, 2008; Sashidhara et al., 2009). Moreover, from a structural point of view, the lead compounds of this type from higher plants perhaps do not intrigue the scientific community so much, because fewer prototype compounds based on new carbon skeleta are represented. Newman and Cragg commented on this matter in 2005: "On the basis of recent experience using the National Cancer Institute (NCI) 60-cell line screen, the potential for the discovery of a new chemotype from plants, comparable to the taxanes or camptothecins, appears to be relatively low. In spite of work covering vascular plants from extensive collections in the tropics over the last 18+ years, no novel chemotypes have, as yet, been reported." (Newman and Cragg, 2005). Arguably, either the taxanes or the camptothecin derivatives may be seen to rival any example of a microbial- or marine-derived lead natural product in terms of the number of new analogs that have entered clinical trials recently (Butler, 2008). However, it is to be hoped that future investigators working on plant-derived anticancer agents will eagerly take on the challenge of discovering new lead compounds that may become of comparable interest to the biomedical community as camptothecin (5) and paclitaxel (4).

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vinblastine (**1**) $\text{R}_1 = \text{CH}_3$ $\text{R}_2 = \text{CH}_3$

vincristine (**2**) $\text{R}_1 = \text{CHO}$ $\text{R}_2 = \text{CH}_3$

1. .

podophyllotoxin (**3**)

2. .

paclitaxel (**4**)

3. .

camptothecin (**5**)

4. .

combretastatin A4 phosphate (**6**) R = OPO₃Na₂
combretastatin A4 (**7**) R = OH

5. .

curcumin (**8**)

6. .

homoharringtonine (9)

7. .

harringtonine (10)

8.

indigo (**11**)

9. .

indirubin (**12**)

10. .

meisoindigo (**13**)

11. .

perillyl alcohol (**14**)

12. .

phenoxodiol (**15**)

13. .

genistein (**16**)

14. .

protopanaxadiol (**17**)

15. .

triptolide (**18**) R = OH

16. .

17..

saprorthoquinone (**20**)

18. .

salvicine (**21**)

19. .

betulinic acid (**22**) R = COOH
betulin (**23**) R = CH₂OH

20. .

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